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7 August 2003 (07.08.2003)

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WO 03/063910 A2

- (51) International Patent Classification<sup>7</sup>: A61K 47/48 (74) Agent: GROS, Florent; Novartis AG, Corporate Intellectual Property, Patent and Trademark Department, CH-4002 Basel (CH).
- (21) International Application Number: PCT/EP03/00803
- (22) International Filing Date: 27 January 2003 (27.01.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
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0202875.1 7 February 2002 (07.02.2002) GB
- (71) Applicant (for all designated States except AT, US): NO-VARTIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SE, SG, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.
- (84) Designated States (regional): Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR).
- (71) Applicant (for AT only): NOVARTIS PHARMA GMBH [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): GARCIA-ECHEVERRIA, Carlos [ES/CH]; Engelgasse 126, CH-4052 Basel (CH).
- Published:  
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title:  $\beta$ -HOMOLYSINE CONJUGATES AND THEIR USE AS TRANSPORT ENHANCER

(57) Abstract: The present invention relates to a conjugate that comprises a) at least one compound to be delivered into or across a biological barrier, b) a delivery-enhancing transporter comprising at least 4  $\beta$ -homolysine residues, especially between 4 and 25  $\beta$ -homolysine residues, c) optionally a linker between the components a) and b), and d) optionally a labelling unit; to the salts of such conjugates; to a pharmaceutical composition comprising said conjugate; to a method for delivery of a compound into or across a biological barrier, the method comprising contacting the barrier with said conjugate; and to a process for the preparation of certain conjugates.

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**DECLARATION AND POWER OF ATTORNEY FOR UNITED STATES PATENT APPLICATION**

☒ Original ☐ Supplemental ☐ Substitute

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name, and

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if more than one name is listed below) of the subject matter which is claimed and for which a United States patent is sought on the invention entitled

**$\beta$  - Homolysine Conjugates and their Use as Transport Enhancer**

the specification of which:

☐ is attached hereto.

☐ was filed on \_\_\_\_\_ as Application No. \_\_\_\_\_  
(day/month/year)

and, if this box (☐) contains an \*

☐ was amended on \_\_\_\_\_  
(day/month/year)

☒ was filed as Patent Cooperation Treaty international Application No.

PCT/ EP03/00803 on 27.01.2003  
(day/month/year)

and, if this box (☐) contains an \*

☐ entered the national stage in the United States and was accorded Application No. \_\_\_\_\_

and, if this box (☐) contains an \*

☐ was amended, subsequent to entry into the national stage, on \_\_\_\_\_  
(day/month/year)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) specifically referred to above and, if this application was filed as a Patent Cooperation Treaty international application, by any amendments made during the international stage (including any made under Patent Cooperation Treaty Rule 91, Article 19 and Article 34).

I acknowledge my duty to disclose information which is material to patentability as defined in 37 C.F.R. 1.56, including, for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or Patent Cooperation Treaty international filing date of the continuation-in-part application.

I hereby claim the benefit under 35 U.S.C. 119(a)-(d) or (f) or 365(b) of any foreign application(s) for patent, inventor's certificate or plant breeder's right certificate listed below and under 35 U.S.C. 365(a) of any Patent Cooperation Treaty international application(s) designating at least one country other than the United States listed below and have also listed below any foreign application(s) for patent, inventor's certificate or plant breeder's right certificate and Patent Cooperation Treaty international application(s) designating at least one country other than the United States for the same subject matter and having a filing date before that of the application the priority of which is claimed for that subject matter:

COUNTRY/REGION (OR P.C.T.)	APPLICATION No.	FILING DATE (day/month/year)	PRIORITY CLAIMED	
Great Britain	0201881.0	28.01.2002	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
Great Britain	0202875.1	7.02.2002	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
			<input type="checkbox"/> Yes	<input type="checkbox"/> No
			<input type="checkbox"/> Yes	<input type="checkbox"/> No
			<input type="checkbox"/> Yes	<input type="checkbox"/> No

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below:

APPLICATION NO.	FILING DATE (day/month/year)
-----------------	---------------------------------

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s) listed below and under 35 U.S.C. 365(c) of any Patent Cooperation Treaty international application(s) designating the United States listed below:

United States Application No.	United States Filing Date (day/month/year)	Status (Pending, Abandoned or U.S. Patent No.)	International Application No. and Filing Date (day/month/year)
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(19) World Intellectual Property  
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(43) International Publication Date  
7 August 2003 (07.08.2003)

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**WO 2003/063910 A3**

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(74) Agent: **GROS, Florent**; Novartis AG, Corporate Intellectual Property, Patent and Trademark Department, CH-4002 Basel (CH).

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PCT/EP2003/000803

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(26) Publication Language: English

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(71) Applicant (*for all designated States except AT, US*): **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

Published:  
— with international search report

(71) Applicant (*for AT only*): **NOVARTIS PHARMA GMBH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(88) Date of publication of the international search report:  
2 September 2004

(72) Inventor; and

(75) Inventor/Applicant (*for US only*): **GARCIA-ECHEVERRIA, Carlos** [ES/CH]; Engelgasse 126, CH-4052 Basel (CH).

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I hereby appoint all of the registered practitioners associated with Customer No. 001095, respectively and individually, as my attorneys and agents, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

If this box (☐) contains an x ☒, I hereby authorize the registered practitioners associated with Customer No. 001095 and any others acting on my behalf to take any action relating to this application based on communications from Corporate Intellectual Property of Novartis International AG, Basle, Switzerland, or an affiliate thereof or a successor thereto, without direct communication from me.

Please send all correspondence relating to this application to the address associated with Customer No. 001095.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

---

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or first joint inventor

Carlos GARCIA-ECHEVERRIA

Inventor's signature

Date

(day/month/year)

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Citizenship

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4052 Basel  
Switzerland

**IMPORTANT:** Before this declaration is signed, the patent application (the specification, the claims and this declaration) must be read and understood by each person signing it, and no changes may be made in the application after this declaration has been signed.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP03/00803

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, CHEM ABS Data, BIOSIS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>GARCIA-ECHEVERRIA C ET AL: "A new Antennapedia-derived vector for intracellular delivery of exogenous compounds." BIOORGANIC &amp; MEDICINAL CHEMISTRY LETTERS, vol. 11, no. 11, 2001, pages 1363-1366, XP002248670 ISSN: 0960-894X abstract; table 1 page 1365, column 1, line 3 - line 5 page 1363, column 1, paragraph 1 page 1363, column 2, line 7 - line 10</p> <p style="text-align: center;">----- -/--</p>	1-16



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the International filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the International filing date but later than the priority date claimed

- \*T\* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

13 August 2003

Date of mailing of the international search report

28/08/2003

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

Berte, M.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/00803

## C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FRACKENPOHL J ET AL: "The outstanding biological stability of beta- and gamma-peptides toward proteolytic enzymes: an in vitro investigation with fifteen peptidases." CHEMBIOCHEM : A EUROPEAN JOURNAL OF CHEMICAL BIOLOGY. 1 JUN 2001, vol. 2, no. 6, 1 June 2001 (2001-06-01), pages 445-455, XP002248671 ISSN: 1439-4227 abstract page 447 - page 448	1-16
A	EP 0 560 730 A (SANDOZ AG ; SANDOZ LTD (CH); SANDOZ AG (DE)) 15 September 1993 (1993-09-15) claims	1-16
A	SEEBACH D ET AL: "The miraculous CD spectra (and secondary structures?) of 'beta!-peptides as they grow longer" HELVETICA CHIMICA ACTA 2001 SWITZERLAND, vol. 84, no. 2, 2001, pages 271-279, XP002248672 ISSN: 0018-019X page 274	16
P,X	GARCÍA-ECHEVERRÍA C ET AL: "beta-Homolysine oligomers: a new class of Trojan carriers." BIOORGANIC & MEDICINAL CHEMISTRY LETTERS. 20 JAN 2003, vol. 13, no. 2, 20 January 2003 (2003-01-20), pages 247-251, XP002248673 ISSN: 0960-894X abstract; tables 1,2 page 251, column 2, paragraph 3	1-16
P,A	FISCHER RAINER ET AL: "A quantitative validation of fluorophore-labelled cell-permeable peptide conjugates: fluorophore and cargo dependence of import." BIOCHIMICA ET BIOPHYSICA ACTA. 31 AUG 2002, vol. 1564, no. 2, 31 August 2002 (2002-08-31), pages 365-374, XP002248674 ISSN: 0006-3002 table 1	1
P,A	WO 02 50102 A (NOVARTIS ERFINDE VERWALT GMBH ; NOVARTIS AG (CH); BAIR KENNETH WALTER ()) 27 June 2002 (2002-06-27) claims 1,3,9	1

# INTERNATIONAL SEARCH REPORT

International application No.  
T/EP 03/00803

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 14-15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/E 3/00803

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0560730	A	15-09-1993	AT 142618 T 15-09-1996
		AU 3406993 A 16-09-1993	
		CA 2091292 A1 11-09-1993	
		CN 1076200 A 15-09-1993	
		CZ 9300361 A3 19-01-1994	
		DE 69304573 D1 17-10-1996	
		DE 69304573 T2 20-03-1997	
		DK 560730 T3 28-10-1996	
		EP 0560730 A2 15-09-1993	
		ES 2090934 T3 16-10-1996	
		FI 931023 A 11-09-1993	
		GR 3021030 T3 31-12-1996	
		HU 63609 A2 28-09-1993	
		HU 9500143 A3 28-07-1995	
		IL 104972 A 05-04-1998	
		JP 2860222 B2 24-02-1999	
		JP 6065175 A 08-03-1994	
		MX 9301298 A1 01-10-1993	
		NO 930830 A 13-09-1993	
		NZ 247084 A 26-09-1995	
		RU 2106356 C1 10-03-1998	
		SG 47059 A1 20-03-1998	
		SK 17093 A3 06-10-1993	
		US 5561112 A 01-10-1996	
		ZA 9301724 A 10-09-1994	
WO 0250102	A	27-06-2002	AU 3459102 A 01-07-2002
			WO 0250102 A2 27-06-2002
			US 2002142966 A1 03-10-2002